CLINICAL TRIALS

TITLE PAGE

TITLE: Barriers to uptake of the hip fracture core outcome set: an international survey of 80 hip fracture trialists.

Running Header: Uptake of core outcome sets

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ABSTRACT

INTRODUCTION: Core outcome sets (COS) are an agreed recommendation to inform the selection of outcome measures in clinical trials. There has been low uptake of the 2014 hip fracture COS. The reasons for this remain unclear. The aim of this study was to understand the reasons for the non-adoption and approaches to increase adoption of the hip fracture COS.

METHODS: Randomised controlled trials (RCTs) from Pubmed (2017-2019) and ClinicalTrials.gov (2015-2019) were identified. Corresponding authors for each identified trial (n=302) were surveyed using five questions on: awareness of the hip fracture COS; reasons for non-adoption; and approaches to increase adoption. Data were analysed descriptively using frequencies, mean and standard deviations.

RESULTS: Fifty-four percent of respondents (n=43) were aware of the concept of COS. Only 15% (n=12) based outcome measure selection on the 2014 hip fracture COS. Key reasons for non-adoption included: authors being unaware and perceived inappropriateness to their trial design. Eighty-six percent (n=69) of respondents agreed the need for increased awareness of COS through research training, academic and clinical journal requirements and funding or publication stipulations. Eighty-eight percent (n=70) of respondents indicated the current COS required revision to focus on trials investigating: people with cognitive impairment, caregivers, rehabilitation, surgical interventions and anaesthetic trial designs.

CONCLUSIONS: Barriers to the adopted of the hip fracture COS centre on education, awareness of the COS and applicability to the breath of hip fracture trial designs. Further consideration should be made to address these, to improve the harmonisation of outcome measures across hip fracture trials.

Keywords: core outcome set; hip; fragility fracture; trial design; survey

BACKGROUND

Hip fracture is a major health and social care challenge for older people. It accounted for nearly 66,000 UK National Health Service (NHS) hospital admissions in 2017.[1] Up to one-third of patients die in the first year post-fracture with one fifth of survivors transitioning to long-term care.[2] To improve outcomes, there is a need for strong and clinically-applicable evidence to inform practice.[3]

A core outcome set (COS) is a list of outcomes to measure effects of interest in clinical trials according to expert stakeholders such as patients, health professionals, commissioners and government bodies, industry and trialists.[4,5] They provide a rationale for the selection of outcomes which are clinically meaningful to these stakeholders but also aid data harmonisation across trials to facilitate meta-analyses. Core outcome sets may be supplemented with additional outcomes pertinent to specific research questions.[4] In 2014, Haywood et al[6] reported a COS for hip fracture trials. This consisted of five key domains: mortality; morbidity; pain; activities of daily living; and health-related quality of life (HRQOL).

Smith et al[7] reported poor uptake of the hip fracture COS across 311 trials published/registered between 1997 and 2018. The rationale for outcome measure selection were not reported across trials, limiting understanding of barriers to the uptake of this recommended COS. The aim of this study was to further understand the barriers to adoption of the hip fracture COS, and identify strategies which may improve the uptake of this COS.

METHODS

Literature Database and Trial Registry Search

Two approaches were taken to construct a dataset of trials whose choice of outcome measure may have plausibly been based on the 2014 hip fracture COS.[6] Firstly, a Pubmed search was undertaken for full trial reports or protocols for people after hip fracture, published from 1st July 2017 to 1st July 2019. The search strategy used was: (((hip) AND fracture)) AND (((randomised controlled trial) OR randomized controlled trial) OR random*). Secondly, the ClinicalTrials.gov trial registry was searched

for eligible trials registered from 1st July 2015 to 1st July 2019. Trials were eligible if they were randomised controlled trials (RCT), which recruited participants who had sustained a hip fracture. The key-term (Hip Fracture) was used with the search filters 'Interventional Trials', 'Phase 3' and 'Phase 4'. Trials were excluded if they were Phase 1 or 2, dose-finding, proof-of-principle or early developmental trials; non-RCT or secondary analyses from trials where the primary trial report was published prior to 2017. Animal and cadaver studies were also excluded. Screening for eligible trials was independently undertaken by two reviewers (JF, TS). Disagreements were resolved through discussion.

Data were extracted from each eligible trial independently by one reviewer (JF) and verified by a second reviewer (TS). Data extracted included: email address for the corresponding author; intervention type (e.g. surgical, rehabilitation, pre-operative); planned sample size; outcome measures; funding source; principal continent of registration; and year of trial registration.

Survey

A survey (**Supplementary File 1**) was sent by email to corresponding authors for each included trial. The five survey questions explored: awareness of COS and the hip fracture COS during trial development; reasons for non-adoption; methods to increase awareness and adoption of the COS; and whether trialists considered the hip fracture COS required revision or extension (if indicated). Demographic characteristics were collected including: trial country of origin; corresponding author job role (clinical, academic or clinical academic), years qualified and highest educational award. Where multiple papers by a single author were identified, a single survey was sent to that author, asking their responses in relation to their most recent paper identified by the search.

Corresponding authors were provided with three weeks to respond to the initial survey. Those who did not respond to the initial email, were sent a reminder email. After a further three weeks, those who had not responded were sent a third and final email, and either the first or last author (alternative to corresponding author) were contacted. After a further three weeks, the survey was closed.

Data Analysis

Data were analysed descriptively using frequencies, percentages, mean and standard deviations (SD). Free-text response options were reviewed by the research team, categorised and then summarised with descriptive statistics. Statistical analyses were undertaken using SPSS Version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

RESULTS

Survey Cohort

In total, 874 individual citations were potentially eligible. After reviewing the titles and abstracts, 572 did not meet the eligibility criteria, providing 302 included trials. Attempts were made to contact all 302 corresponding authors. Of these 33 (11%) were not contactable. Of the 269 emails sent, 80 (30%) authors replied. These responses are included in this analysis.

Trial and Author Characteristics

A summary of the included trials and author characteristics is presented in **Table 1**. The 80 RCTs consisted of 20 (25%) surgical trials, 22 (28%) perioperative intervention trials, 18 (23%) anaesthetic trials and 18 (23%) rehabilitation trials. The majority were funded by research councils (non-industry) (n=39; 49%). Trials most frequently originated from Europe (n=52; 65%), followed by North America (n=17; 21%). Fifty-four percent (n=43) of respondents were clinical academics.

Of the 80 trials analysed, 16 (20%) satisfied the hip fracture COS. The core domain most frequently reported was mortality (n=70; 88%). Approximately half of trials measured activities of daily living (n=40; 50%), mobility (n=43; 54%) and HRQOL (n=39; 49%). Pain was measured in 30 (38%) trials. The mean number of domains reported was three (SD: 1.6).

Core Outcome Set Non-Adoption

Reasons for not using the hip fracture COS are itemised in **Table 2**. Eleven respondents (14%) used the Haywood et al[6] hip fracture COS as the basis of their outcome measure selection. Forty-three (54%) respondents were aware of COS (in principle) to inform the selection of outcome measures in clinical

trials. The most frequently reported reasons for non-adoption of the hip fracture COS were: being unaware of this COS (n=31; 39%); the research protocol being prepared prior to publication of the COS (n=19; 24%); the hip fracture COS not being specific for their trial designs (n=8; 10%).

Methods of Increasing Hip Fracture Core Outcome Set Awareness

Table 2 summarises the recommendations from respondents on how awareness of the hip fracture COS could be increased. The most frequently reported methods to increase awareness were: to incorporate into research training (n=47; 59%); across clinical and academic forums (n=41; 51%); and setting COS as a requirement for publication in journals (n=29; 36%). Twenty-three (29%) respondents recommended the use of COS should be mandated by funding organisation. Ten (13%) respondents reported that nothing was required to increase awareness.

Respondents were asked to comment on recommended areas where they considered the current hip fracture COS may require extension or revision. Eleven respondents (14%) recommended that no revision or extension was required; six (8%) respondents had no opinion. The remaining 63 (79%) respondents prioritised a COS extension for: trials recruiting people with cognitive impairment (n=43; 59%); rehabilitation trials (n=28; 35%); surgical intervention trials (n=27, 34%); and trials recruiting caregivers (n=26; 33%). Nineteen participants (24%) recommended an extension for anesthetic trials. Six (8%) respondents recommended that further work was required on developing the instrument selection of the Haywood et al[6] COS.

DISCUSSION

The findings indicate that the 2014 hip fracture COS[6] is poorly adopted due to low awareness of its presence and value, and potential issues around its applicability for the heterogeneity of hip fracture trials. Trialists have recommended strategies to address these shortcomings including increasing awareness and strategies to promote the adoption in future trials, and suggestions on where further research may be undertaken to evolve this COS.

Previous authors have acknowledged the challenges of COS adoption. Smith et al[7] reported the uptake of the hip fracture COS at 38%. The highest annual adoption of the hip fracture COS was 24% in trials registered in 2009 compared to 0% for trials registered in 2017 and 2018. Kirkham et al[9]

reported an important justification which trialists used for not adopting the COS for rheumatoid arthritis. They suggest that the COS was not applicable to their specific trial populations.[9] This is a similar view this study's hip fracture trialists who suggested tailored COS were required for populations with cognitive impairment. This questions either the universality of a COS for its intended population or the attitudes of trialists regarding how additional measures can supplement a COS, which is accepted practice by COS methodologists.[4,5]

Trialists who responded to this survey suggested a need for increasing awareness of COS. Kirkham et al[9] suggested the principal factor to increase uptake for COS was mandating their use by regulatory authorities and funders. Whilst this may be possible for trials of medicinal products requiring regulatory approvals, this may be more challenging for rehabilitation and care pathway research which are frequently undertaken in this field. Trialists should encourage funders to mandate in funding applications, and clinical guideline developers, to establish expectations of COS usage. This will provide further impetus for trialists to adopt COS. There may also be a responsibility of COS developers to increase awareness of their COS work through wider dissemination strategies. To the author's knowledge, Haywood et al's[6] hip fracture COS was disseminated through peer-review publication alone. Wider dissemination activities, such as collaborations with national organisations, social media publicity and presenting findings through wider academic and clinical outlets, would be advantageous. This would both increase awareness of the value of this COS, but also COS in general.

The majority of respondents considered extensions of the hip fracture COS warranted for specific sub-populations or interventions. This is based on the heterogeneity in trial designs, interventions and within the population which exists in hip fracture research. O'Donnell et al[10] reported the development of a COS for anaesthesia trials on perioperative morbidity and mortality following hip fracture surgery. Further extensions may be warranted for trials recruiting participants with cognitive impairment, rehabilitation and surgical trials. Multi-disciplinary working groups of clinicians, academics, policymakers, and patient/public partners should consider these as research priorities, to improve the harmonisation and evidence-led approach to outcome selection in hip fracture trials.

The current hip fracture COS provides clear guidance on which domains should be assessed in hip fracture trials [6]. However there remains uncertainty as to which instruments should be used to measure these domains. Whilst there have been recommendations in routinely collected data sets such as the UK National Hip Fracture Database[11] that instruments such as the EQ-5D[12] should be used to measure HRQOL, no formal assessment has been made of the psychometric properties of this or other instruments in this population to provide guidance on instrument selection. A priority to aid

trialists adopting this COS may therefore be such work, providing clearer guidance on 'how' this COS can be utilised.

This study is not without limitations. Firstly, the study response rate was 30%. Whilst this is considered reasonable for electronic surveys,[13] there remains uncertainty as to whether the responses were based on a self-selecting sample of trialists and if this is representative of all hip fracture researchers. Secondly, the focus of this survey was regarding the hip fracture COS. Accordingly it is only possible to generalise towards this. However, previous literature has identified similar barriers to COS uptake for osteoarthritis,[14] sepsis,[8] and dermatology[15] trials. Thirdly, pre-survey work based on Smith et al's[7] COS uptake analysis and piloting of this study's survey suggested that awareness of the COS may be a major reasons for non-adoption. Whilst awareness was a major factor, for the purposes of not burdening respondents, we omitted asking deeper questions related to other potential barriers such as lack of trust. Qualitative study exploring trialist's wider perceived barriers for adoption of this COS and ways to increase adoption may be a valuable addition to the evidence-base. Finally, the COS was published in 2014. Whilst only trials published as protocols or reported from 2017 were eligible, 24% of trialists reported that their trial designs were finalised prior to 2014. This may account in part to the low uptake.

CONCLUSION

This study supports the previous evidence that the hip fracture COS is poorly adopted in hip fracture trials. This is largely due to a low awareness of this COS, trialist perceiving that they were not specific to their trial designs, or trial designs pre-dated the 2017 publication of the COS. Work is now warranted to increase awareness of this COS and to develop the instrument-selection guidance. Further research may also be required to develop the COS for specific hip fracture trial populations or interventions.

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Ethical approvals: No ethical approvals were required to undertake this study.

Conflicts of interest: No author has any conflicts of interest to declare.

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Table 1: Characteristics of included trials and corresponding authors

Characteristic	Frequency (%) or Mean (SD)
Intervention Type	
Rehabilitation	18 (23)
Surgical	20 (25)
Perioperative General	22 (28)
Pre-operative	2 (3)
Intra-operative (non-surgical)	18 (23)
Funding Source	
Research Council	39 (49)
Industry	6 (8)
Mixed (Research Council & Industry)	3 (4)
Not stated	32 (40)
Principal continent of registration	
Europe	52 (65)
Asia	6 (8)
North America	17 (21)
South America	1 (1)
Australasia	1 (1)
Africa	0 (0)
No stated	3 (4)
Year of Registration	
1992-1996	1 (1)
1997-2001	2 (3)
2002-2006	9 (11)
2007-2011	27 (34)
2012-2016	35 (44)
2017-2018	6 (7)
Core Outcome Set Domain and Set Satisfaction *	
Mortality	70 (88)
Pain	30 (38)
ADLs	40 (50)
Mobility	43 (54)
HRQoL	39 (49)
Number of domains reported (mean; SD)	2.9 (1.6)
Core Outcome Set Compliant	16 (20)
Corresponding Author: Job Type	
Clinical academic	43 (54)
Academic	14 (18)
Clinical	9 (11)
No response	14 (17)
Corresponding Author: years qualified	
Years (mean; SD)	21 (11.1)
No response	34 (43)
Corresponding Author: highest educational award	
Doctorate (e.g. PhD, MD, DM, DPhil)	62 (78)
Masters Degree (e.g. MSc, MA)	7 (9)
Pre-Registration Medical Degree (e.g. MBBS)	3 (4)
No response	8 (9)

* percentages add up to more than 100 as respondents could select more than one option.

ADLs – activities of daily living; DM – Doctor of Medicine; DPhil – Doctor of Philosophy; HRQoL – health-related

quality of life; MA – Masters in Arts; MBBS – Bachelor of Medicine and Bachelor of Surgery; MD – Doctor of Medicine; MSc – Masters in Sciences; PhD – Doctor of Philosophy; SD – standard deviation

Table 2: Table to summarise the survey responses (n=80 respondents) from corresponding authors of included trials.

Survey Question	Frequency (%)
Reason for not using hip fracture core outcome set	
Unaware of the existence of the hip fracture COS	31 (39)
Study development prior to 2014	19 (24)
Not suitable for trial design	8 (10)
Outcomes determined by existing dataset processes	3 (4)
No response	19 (23)
Methods of increasing awareness*	
Funding application requirement	23 (29)
Publication and journal requirement	29 (36)
Increase awareness in research training	47 (59)
Increase publicity across social media and clinical/academic forums	41 (51)
Nothing – there is sufficient awareness	10 (13)
Review of research practice	2 (3)
Increased research in this area	1 (1)
No opinion	4 (5)
Recommended areas for hip fracture core domain set extension*	
Participants with cognitive impairment	43 (54)
Rehabilitation trials	28 (35)
Surgical intervention trials	27 (34)
Caregiver participants	26 (33)
Anesthetic trials	19 (24)
No extension	11 (14)
Other: development of instrument selection	6 (8)
Other: Health economics	2 (3)
Other: Nursing home	1 (1)
Other: No opinion	6 (8)

* percentages add up to more than 100 as respondents could select more than one option.

COS – core outcome set; N – number

Supplementary Table 1: Corresponding author email questions

Question Number	Question	Response Option
1	Are you aware of the concept of a Core Outcome Set to inform the selection of outcome measures in clinical trials?	• YES / NO
2i	Did the Haywood et al (2014) hip fracture Core Outcome Set inform the selection of the outcome measures used in your trial? (If YES go to Question 4)	• YES / NO
2ii	*If NO*, why was this the case? Was it because:	• Unaware of the existence of this Core Outcome Set • Used a different Core Outcome Set (if so, please provide the reference for this) • Was aware of the Core Outcome Set but felt it was not suitable for the intervention of interest (if so, please explain why) • Was aware of the Core Outcome Set but felt it was not suitable for the population (if so, please explain why) • Was not a requirement for the funder, so choose not to use • Was not a requirement for the regulatory authority, so chose not to use • Other (please state) …
3	What could be done to increase awareness of the Hip Fracture Core Outcome Set?	• Nothing, there is sufficient awareness of the Hip Fracture Core Outcome Set. • Explicit requirement in funding applications • Explicit requirement in publications and journals • Increased awareness of Core Outcome Sets in research training • Increased publicity across social media and clinical/academic forums • Other (please state)…
4	If an update to the existing Core Domain Set was proposed, what areas should these be focused on?	• No extension required, a single Core Outcome Set for all hip fracture trials is sufficient • Trials recruiting people with cognitive impairment • Trials recruiting caregivers

		• Surgical intervention trials • Anaesthetic trials • Rehabilitation trials
5i	*Correspondent author details: C*ountry you are based in:	• Free-text
5ii	*Correspondent author details:* Role (*please highlight your response*):	• Academic • Clinician • Clinical academic • Other (please state) …
5iii	*Correspondent author details:* years qualified	• Free-text
5iv	*Correspondent author details:* highest educational attainment (*please highlight your response*):	• BSc/BA • MSc/MA • PhD/MD/DPhil • Other (please state) …